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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,345	09/04/2003	C. Steven McDaniel	5842-00601	6570

62754 7590 03/27/2009

DAFFER MCDANIEL, LLP
P.O. BOX 684908
AUSTIN, TX 78768-4908

EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
03/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,345	MCDANIEL, C. STEVEN	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 27, 2008 & January 30,2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0808;1008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1, 15-28, 31-35, 37-52, 55-63, 65-67, 69-75, 79-108, 110-256, 272, 309, 319-359, 361,362, 365- 373, and 376-392 .
Continuation of Disposition of Claims: Claims withdrawn from consideration are 28,31-35,37-52,55-63,69-71,90-93,101,103-108,120,136-179,183-216,218,243-250,256,322,325,328-342,357-359 and 386-388.

Continuation of Disposition of Claims: Claims rejected are 1,15-27,65-67,72-75,79-89,94-100,102,110-119,121-135,180-182,217,219-242,251-255,272,309,319-321,323,324,326,327,343-356,360-362,365-373,376-385 and 389-392.

DETAILED ACTION

Applicant's filing of August 27, 2008, in response to the action of February 27, 2008, is acknowledged. Applicant's election of January 30, 2009, in response to the Restriction requirement, mailed October 31, 2008, is acknowledged. The invention previously examined in the Action of February 27, 2008 was directed to an aqueous paint comprising an organophosphorus hydrolase, wherein the paint forms a film under ambient conditions. It is acknowledged that, with the response of January 30, 2009, Applicants have affirmed their election of an aqueous paint comprising an organophosphorus hydrolase, wherein the paint forms a film under ambient conditions. With the response of January 30, 2009, Applicants confirmed or further elected, without traverse:

- o A Flavobacterium sp opd gene product
- o Co2+ ion
- o Film formation at -10°C - 40°C/ambient conditions
- o Liquid/solvent component of water
- o Without any inorganic compounds
- o Without any organic components
- o A thermoplastic binder
- o A combination of a filler and a preservative
    - • the preservative being a bactericide
- o No plasticizer

The currently elected invention is directed to an aqueous paint comprising an organophosphorus hydrolase that is a Flavobacterium sp opd gene product comprising a Co2+

ion, wherein the paint comprises a thermoplastic binder, a filler and a bactericide preservative, and the paint forms a film under ambient conditions, and wherein the paint does not have additional inorganic compounds, organic compounds, or a plasticizer.

Based on Applicant's filing of August 27, 2008, Claims 1,15-17, 43, 63, 65, 67, 69, 81, 82, 86, 222, 253, 254, 313-319, 344, 351-353, 355, 356, 360, 368-371, and 391 are amended, Claims 13, 14, 313-318, 364, and 375 are canceled, and Claims 1, 15-28, 31-35, 37-52, 55-63, 65-67, 69-75, 79-108, 110-256, 272, 309, 319-359, 361,362, 365- 373, and 376-392 are pending in the case. Claims 28, 31-35, 37-52, 55-63, 69-71, 90-93, 101, 103-108, 120, 136-179, 183-216, 218, 243-250, 256, 322, 325, 328-342, 357-359, and 386-388 are herein withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are hereby examined.

Claims-Objections

Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are objected to for reciting non-elected subject matter.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

Enablement

Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the paints comprising an organophosphorus hydrolase as described in Examples 3-5, does not reasonably provide enablement for paints comprising any protein, having any structure, and having any organophosphorus hydrolase activity as well as any thermoplastic binder, any filler, and any bactericide preservative. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that the above rejection encompasses maintaining the rejection of Claims 1, 67, 72-75, 79-83, 88, 89, 94-97, 110-112, 126-131, 180-182, 217, 251, 252, 319, 320, 323, 324, 343, 344, 351-354, 365, 368-370, 376, 380-385 and 391 under 35 U.S.C. 112, first paragraph/enablement, for reasons stated in the prior actions. Rejection of additional claims and additional reasons for rejection are based on Applicants' amendments. A summary of the rejection of Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 is presented as follows.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement

and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are so broad as to encompass any paint comprising one or more of the following: (i) any protein, having any structure, and having organophosphorus hydrolase activity, (ii) any compound or composition, having any structure, and having thermoplastic binder activity, (iii) any compound or composition, having any structure, and having filler activity, and (iv) any compound or composition, having any structure, and having any bactericide preservative activity. The claims further encompass one or more of the following functional limitations: (i) forming a solid film of a certain thickness by loss of a volatile component under ambient conditions, (ii) forming a temporary film, (iii) is effective as a coating on a wide variety of sufaces, (iv) has a specific range of densities, (v) is corrosion resistant, (vi) the organophosphorus hydrolase activity is retained for up to a year after surface application, (vii) the organophosphorus hydrolase cleaves any chemical warfare agent and/or any pesticide, (viii) the organophosphorus hydrolase cleaves multiple chemical warfare agents and/or multiple pesticides, (ix) the organophosphorus hydrolase binds to a living organism and (x) the coating is self-cleaning.

The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of paints, comprising any organophosphorus hydrolase, any thermoplastic binder, any filler, and any bactericide preservative, as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired organophosphorus hydrolase activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. Likewise, since the structure of any compound determines it's ability to function as a thermoplastic binder, a filler, and a bactericide preservative, predictability of which changes can be tolerated in known active compound requires a knowledge of and guidance with regard to which parameters of the structures, if any, are tolerant of modification and which must be conserved, including a detailed knowledge of the ways in which any compounds structure relates to its function as a thermoplastic binder, a filler, or a bactericide preservative. However, in this case the disclosure is limited to the organophosphorus hydrolase as described in Examples 3-5, and the fillers disclosed in Example 14.

While methods for altering the structure of proteins and compounds, as well as methods for testing proteins for organophosphorus hydrolase activity and compounds for activity as a thermoplastic binder, a filler, or a bactericide preservative, are known in the art, it is not routine in the art to screen an essentially unlimited number of proteins and compounds for the desired activities. Furthermore, the positions within a protein's sequence where amino acid

modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein or compound to diminish with each further and additional modification, e.g. multiple substitutions/alterations.

The specification does not support the broad scope of Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392, which encompasses all paints comprising one or more of the following: (i) any protein, having any structure, and having organophosphorus hydrolase activity, (ii) any compound or composition, having any structure, and having thermoplastic binder activity, (iii) any compound or composition, having any structure, and having filler activity, and (iv) any compound or composition, having any structure, and having any bactericide preservative activity. In addition, the specification does not support the broad scope of paints encompassing one or more of the following functional limitations: (i) forming a solid film of a certain thickness by loss of a volatile component under ambient conditions, (ii) forming a temporary film, (iii) is effective as a coating on a wide variety of sufaces, (iv) has a specific range of densities, (v) is corrosion resistant, (vi) the organophosphorus hydrolase binds to a living organism, (vii) the organophosphorus hydrolase activity is retained for up to a year after surface application, (viii) the organophosphorus hydrolase cleaves any chemical warfare agent and/or any pesticide, (ix) the organophosphorus hydrolase cleaves multiple chemical warfare agents and/or multiple pesticides, and (x) the coating is self-cleaning.

The specification does not support the broad scope of Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 because the specification does not establish: (A) the structure of all proteins having the desired organophosphorus hydrolase activity, including the functional limitations of binding to a living organism, activity is retained for up to a year after surface application, cleaves any chemical warfare agent and/or any pesticide, and cleaves multiple chemical warfare agents and/or multiple pesticides; (B) regions of the protein structure which may be modified without affecting the desired activities; (C) the general tolerance of the desired activities to modification of the protein structure and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological functions for the organophosphorus hydrolase; (E) the structure of all compounds/compositions having the desired thermoplastic binder activity, filler activity, or bactericide preservative activity; (F) regions of the compound/composition structure which may be modified without affecting the desired activities; (G) the general tolerance of the desired activities activity to modification of the compound/composition structure and extent of such tolerance; (H) a rational and predictable scheme for modifying any compound/composition with an expectation of obtaining the desired biological functions; (I) the structure/composition of all paints forming a solid film of a certain thickness by loss of a volatile component under ambient conditions, (J) the structure/composition of all paints forming a temporary film, (K) the structure/composition of all paints effective as a coating on a wide variety of surfaces, (L) the structure/composition of all paints having a specific range of densities, (M) the structure/composition of all paints that are corrosion resistant;

(N) how the structure/composition of any paint may, or may not be altered and still retain the desired activity to form a solid film of a certain thickness by loss of a volatile component under ambient conditions, form a temporary film, be effective as a coating on a wide variety of surfaces, having a specific range of densities, and being corrosion resistant; (O) the general tolerance of the structure/composition of any paint to modification and extent of such tolerance in maintaining the characteristics listed in (N); (P) a rational and predictable scheme for modifying the structure/composition of any paint while still maintaining the characteristics listed in (N); and (Q) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of paints having the characteristics described in (A)-(Q), above. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of paints having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection be withdrawn, Applicants provide the following arguments, filed August 27, 2008, which are relevant to the above.

(A) In response to a previous Office Action mailed May 18, 2007, with a limitation which the Examiner acknowledged as being enabled and supported by the written description of

the specification, particularly that the claimed coatings comprise an enzymatically active organophospho hydrolase (see page 6, lines 5-6 of the Office Action mailed May 18, 2007), the claims had been previously amended.

(B) The claims of the case have been amended to recite "an enzymatically active esterase classified in an enzyme subclass designated by Enzyme Commission number EC 3.1.8".

(C) All proteins of which the inventors were aware at the time of filing having the desired activity of enzyme commission number EC 3.1.8 are disclosed in the specification and are described in detail, particularly in paragraphs [0129] to [0153], [0168] to [0191], [0202], [0205], [0213], [0215], [0216], [0226], [0236], [0237], [0239], [0240], [0676], [0688], and [0718].

Paragraphs [0140] to [0144] specifically disclose organophosphorus hydrolase (e.g., Agrobacterium radiobacter P230 organophosphate hydrolase, Flavobacterium balustinum parathion hydrolase, Pseudomonas diminuta phosphotriesterase, Flavobacterium sp opd gene product, and Flavobacterium sp. parathion hydrolase opd gene product).

(D) The specification provides ample guidance as to modifications for producing catalytically active variations in enzyme sequence and structure. For example, paragraph [0143] references the crystal structure of Pseudomonas OPH, and describes structural analogues where active site metal ions are substituted to alter activity. Paragraph [0158] describes "... residues at or near the active site ... contribute to a chemical reaction ... to produce enzymatic activity ...". Furthermore, paragraphs [0159] to [0162] and [0170] to [0171] describe identification techniques (e.g., chemical reaction, mutation, X-ray crystallography, NMR, computer based modeling) for an amino acid whose alteration would alter enzymatic activity (e.g., OPH amino acids His55, His57, His 201, His230, Asp301, Lys169, Asp232, Asp233, Asp235, Asp253, His354, His254,

His257, Trpl31, Phe132, Leu271, Phe306, Tyr309, Gly60, Ilel06, Leu303, Ser308, Cys59, Ser61, Met317; and corresponding amino acids by comparison to Agrobacterium radiobacter p230 OPH).

(E) Paragraph [0163] describes replacing an identified amino acid with conservative substitutions (e.g., "... replacing an amino acid side chain with one similar in charge ... hydrophobicity ... shape ... size ... chemical type ...") as well as the guidance of amino acid substitutions via the hydropathic index and hydrophilicity values of amino acids (e.g., "an amino acid is being conservatively substituted ... the difference is preferably within +/- 2 ..."). In addition, paragraph [0163] conversely teaches the use of non-conservative amino acid side chain substitutions, based on an identified amino acid of interest, to produce functional equivalents. Furthermore, paragraphs [0172] to [0181] teach specific OPH sequence analogues that produce catalytically active enzymes classified in EC 3.1.8 (e.g,. H55C, H57C, C59A, G60A, S61A, 1106A, 1106G, W131A, W131F, W131K, F132A, F132H, F132Y, L136Y, L140Y, H201C, H230C, H254A, H254R, H254S, H257A, H257L, H257Y, L271A, L271Y, L303A, F306A, F306E, F306H, F306K, F306Y, S308A, S308G, Y309A, M317A, M317H, M317K, M317R, H55C/H57C, H55C/H201C, H55C/H230C, H57C/H201C, H57C/H230C, A80V/S365P, I106A/F132A, I106A/S308A, I106G/F132G, I106G/S308G, F132Y/F306H, F132H/F306H, F 132H/F306Y, F 132Y/F306Y, F 132A/S308A, F 132G/S308G, L 182S/V310A, H201 C/H230C, H254R/H257L, H55C/H57C/H201 C, H55C/H57C/H230C, H55C/H201 C/H230C, I 106A/F 132A/H257Y, I 106A/F 132A/H257W, I 106G/F 132G/S308G, L 130M/H257Y/I274N, H257Y/I274N/S365P, H55C/H57C/H201 C/H230C, I 106G/F 132G/H257Y/S308G, or A14T/A80V/L185R/H257Y/I274N).

(F) Paragraph [0164] describes chemical alterations that may be used to modify an amino acid to produce functional equivalents, and paragraphs [0165] to [0167] describe production of longer or shorter amino acid sequences (e.g., removal of an N-terminus amino acid sequence from OPH to enhance production in Escherichia coli) to produce enzymes retaining activity. The specification further provides numerous additional examples of these types of modifications to produce active enzymes, including active site metal ion substitutions (e.g., Co2+, Fe2+, Cu2+, Mn2+, Cd2+,or Ni2+ at) of OPH at paragraph [0169]. Moreover, the specification teaches combinations of metal ion substitutions with sequence analogues in paragraph [0173] and [0174] as well as removal of terminus sequences and adding peptide sequences (e.g., fusion proteins) and/or OPH sequence analogues in paragraphs [0182] to [0186].

(G) Further examples of producing enzymes within subclass EC 3.1.8 having such modifications are disclosed in the specification, such as the identification of paroxonase amino acids involved in enzymatic activity (e.g., E32A, E48A, E52A, D53A, D88A, D107A, H114N, D121A, H133N, H154N, H160N, W193A, W193F, W201A, W201F, H242N, H245N, H250N, W253A, W253F, D273A, W280A, W280F, H284N, H347N) via chemical modification of enzymes, cross species sequence comparisons, and site directed mutagenesis in paragraphs [0187] to [0188]. In addition, the identification of Squid-type DFPase amino acids involved in enzymatic activity (e.g., H181N, H224N, H274N, H219N, H248N, or H287N) is described in paragraphs [0189] to [0191]. Techniques for additional terminal sequence truncations and additions (e.g., fusion proteins) are described in paragraphs [211] to [0231], with numerous examples provided (e.g., fusion proteins, tags, fusion partners) in paragraphs [202], [0213], [0215], [0216], [0226], [0236], [0237], [0239], [0240] and [0688].

(H) Applicants respectfully disagree that one skilled in the art is unnecessarily and improperly left to experimentation which is extensive and undue. As noted above, the specification provides ample guidance with respect to the direction in which experimentation should proceed to determine whether an enzyme exhibits enzymatic activity of an esterase classified in EC 3.1.8 in a coating. Assays for determining enzymatic activity are described at paragraphs [0636] to [0646], [0676], [0680], [0689] to [0698], and [0719] to [0722]. The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands', 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. United States v. Telectronics Inc., 857 F.2d 778,785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

(I) Applicant traverses the Examiner's declaration that "... it is not routine in the art to screen for multiple substitutions or multiple modifications ..." (Office Action, page 5). On the contrary, screening procedures are customary when testing enzyme activity. Support for such an assertion may be found, for example, in paragraph [0181] of the specification: It is also possible

to produce a mutant enzyme with an enhanced enzymatic property against a specific substrate by evolutionary selection rather than rational design. Such techniques can screen hundreds or thousands of mutants for enhanced cleavage rates against a specific substrate. The mutants identified may possess substitutions at amino acids that have not been identified as directly comprising the active site, or its binding subsites, using techniques such as NMR, X-ray crystallography and computer structure analysis, but still contribute to activity for one or more substrates. For example, selection of OPH mutants based upon enhanced cleavage of methyl parathion identified the A80V/S365P, L 182S/V310A, I274N, H257Y, H257Y/1274N/S365P, L 130M/H257Y/1274N, and A14T/A80V/L 185R/H257Y/1274N mutants as having enhanced activity. Amino acids Ile274 and Val310 are within 10 .ANG. of the active site, though not originally identified as part of the active site from X-ray and computer structure analysis. However, mutants with substitutions at these amino acids demonstrated improved activity, with mutants comprising the I274N and H257Y substitutions particularly active against methyl parathion. Additionally, the mutant, A14T/A80V/L185R/H257Y/I274N, further comprising a L185R substitution, was most active having a 25-fold improvement against methyl parathion (Cho, C. M.- H. et al., 2002). For at least the reasons noted above, it is asserted that the specification enables one skilled in the art to make and use the limitations of the present claims. In addition, it is asserted that the specification conveys to one skilled in the art that the inventor had possession of the claimed subject matter and, therefore, the written description requirement is satisfied for the present claims. Accordingly, removal of 35 U.S.C. § 112, first paragraph rejections of the claims is respectfully requested.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is unclear to the examiner what is being argued here. The Office Action mailed May 18, 2007, page 6, lines 5-6, merely reiterates Applicants' prior argument:

> "(C) The specification is enabling for a broader scope of coatings than just a paint comprising enzymatically active organophospho-hydrolase."

(B) Reply: It is acknowledged that the claims have been so amended. The scope of the proteins encompassed by "an enzymatically active esterase classified in an enzyme subclass designated by Enzyme Commission number EC 3.1.8" is even broader than the scope encompassed by any organophosphorus hydrolase. Thus, claims reciting an enzymatically active esterase classified in an enzyme subclass designated by Enzyme Commission number EC 3.1.8 are rejected under 35 U.S.C. 112, first paragraph/enablement for the reasons explained above and in the prior actions.

(C) Reply: It is acknowledged that the specification describes the activities of a number of enzymes encompassed within EC 3.1.8. However, said description of functions fails to provide the public with the structures of all encompassed proteins.

Likewise, it is acknowledged that the specification describes the activities of a number of enzymes encompassed by any "organophosphorus hydrolase", of the elected invention. However, said description of functions fails to provide the public with the structures of all encompassed proteins, which includes recombinant proteins that are sequence or structural analogs.

(D) Reply: It is acknowledged that paragraph [0143] discloses that Benning et al, 1994 teaches the crystal struture of a Pseudomonas organophosphorus hydrolase, and that the teachings therein provide some guidance as to residues involved in the binding of divalent metal ions.

It is acknowledged that paragraphs [0159-0162] describe techniques that can be used for identification of residues important for the desired activities; thereby leaving to the public the burden of using said techniques for said identification.

It is acknowledged that paragraphs [0170-0171] lists, by positions number, six residues identified as coordinating the binding of divalent metal ions, one residue involved in nucleophilic attack, and several thought to aid in binding of substrate. However, without references to a specific sequence, said list of position numbers is indefinite. In addition, structural analysis of a single organophosphorus hydrolase does not provide evidence that all organophosphorus hydrolases will use the same residues. The art teaches that the effects of altering the structure of organophosphorus hydrolases on the activity remained unpredictable at the time of filing. Thus, it is taught that a cryptic functional allosteric site in a organophosphorus hydrolase was subsequently identified (Grimsley et al, 2005, pg 178, parg 3-5), proteins having up to 90% identity with an active organophosphorus hydrolase can have a different function (Yang et al, 2003; Fig 4), allosteric regulation is substrate-dependent (Yang et al, 2003; Table III), and mutation of a single residue converts a carboxylesterase to an organophosphorus hydrolase (Newcomb et al, 1997). Grimsley et al, specifically teach:

> "The combined kinetic and structural data on P. diminuta OPH indicate that the binding of various substrates and inhibitors to the active site is exquisitely sensitive to the structure of the active site. Mutation of "second-shell" amino acids or substitution of different metal cations can drastically alter the substrate specificity…" (pg 178, parg 3)

Paragraph [0158] merely defines "at or near" as being within 15A.

(E) Reply: It is acknowledged that paragraph [0163] exemplifies, but does not define, some conservative substitutions. It is also acknowledged that paragraphs [0172-0181] teach

some desired amino acid substitutions. However, without reference to a specific sequence, said substitutions are indefinite.

(F) Reply: It is acknowledged that methods for chemical modification of proteins and identifying active fragments were known in the art. It is also acknowledged that paragraph [0169] directs the skilled artisan to Omburo et al, 1992 and Kolakoski et al, 1997, which teach that the activity of an OPH is dependent on the metal cation bound. It is acknowledged that paragraphs [0173-0174] teach substitution of various histidine residues affect the metal cation specificity, which would provide some guidance to the artisan if reference to a specific sequence was made.

(G) Reply: It is acknowledged that the specification lists some substitutions in a paroxonase or DFPase without reference to specific sequences.

(H) Reply: It is acknowledged that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In the instant case, the claims encompass a paint comprising any protein, having any structure, wherein the protein has OPH activity against any substrate and further has the functional limitations of (i) binds to a living organism, (ii) the activity is retained for up to a year after surface application, (iii) the organophosphorus hydrolase cleaves any chemical warfare agent and/or any pesticide, and (iv) the organophosphorus hydrolase cleaves multiple chemical warfare agents and/or multiple pesticides. While the specification provides some guidance as to residues important for maintaining organophosphorus hydrolase activity against some substrates in some enzymes, the specification fails to provide guidance on which residues may, or may not, be

altered in any OPH and still retain the functional limitations of (i)-(iv). Moeover, as explained above (D), the art teaches that the relationship between the structure and function of OPH proteins remained unpredictable. While methods for making and testing any protein for the desired activities, said making and testing the essentially unlimited number of proteins represents undue experimentation for the reasons explained herein and in the prior actions.

(I) Reply: See (H), above.

Written Description

Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of paints comprising any protein, having any structure, and having any organophosphorus hydrolase activity as well as any thermoplastic binder, any filler, and any bactericide preservative, wherein the paint has the further functional limitations of (i) forming a solid film of a certain thickness by loss of a volatile component under ambient conditions, (ii) forming a temporary film, (iii) is effective as a coating on a wide variety of sufaces, (iv) has a specific range of densities, (v) is corrosion resistant, (vi) is self-cleaning (vii) the organophosphorus hydrolase binds to any living organism, (viii) the organophosphorus hydrolase activity is retained for up to a year after surface application, (ix) the organophosphorus hydrolase cleaves any chemical warfare agent and/or any pesticide, and (x) the organophosphorus hydrolase cleaves multiple chemical warfare agents and/or multiple

pesticides. The specification teaches no representative species of such paints. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionalities of stated above. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

It is noted that the above rejection encompasses maintaining the rejection of Claims 1, 67, 72-75, 79-83, 88, 89, 94-97, 110-112, 126-131, 180-182, 217, 251, 252, 319, 320, 323, 324, 343, 344, 351-354, 365, 368-370, 376, 380-385 and 391 under 35 U.S.C. 112, first paragraph/written description, for reasons stated in the prior actions. Rejection of additional claims and additional reasons for rejection are based on Applicants' amendments.

In support of their request that said rejection be withdrawn, Applicants provide the arguments set forth in (A)-(I), above. These arguments are not found to be persuasive for the reasons explained above and in the prior actions; the specification fails to describe the recited invention in a manner such that the skilled artisan would appreciate that they were in possession at the time of filing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Rejection of Claims 1, 67, 72-75, 79, 80, 82, 83, 88, 89, 94-97, 110-112, 126-131, 180-182, 217, 252, 319, 320, 323, 324, 343, 344, 351-354, 365, 368-370, 376, 380-385 and 391 under 35 U.S.C. 103(a) as being unpatentable over Bonaventura et al, 1999 in view of Cheng et al, 1999, for the reasons explained in the prior actions, is maintained. Claims 15-19, 21, 22, 24, 84-87, 98, 113-119, 121-125, 132, 219-225, 227, 228, 231, 232, 236-238, 253-255, 272, 355, 356, 360-362, 366, 367, 371-373, 377-379, 390, and 392 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaventura et al, 1999 in view of Cheng et al, 1999, for the same reasons. A summary of said rejection is provided, as follows.

Bonaventura et al teaches paint comprising a variety of enzymes (Example 1). Bonaventura et al do not teach paint comprising an organophosphorus hydrolase. Cheng et al teaches a variety of liquid compositions comprising an Altermonas organophosphorus hydrolase. It would have been obvious to a person of ordinary skill in the art to modify the paints of Bonaventura et al by incorporating the organophosphorus hydrolase of Cheng et al. Motivation to do so derives from the desire to treat a surface for organophosphates, known toxic agents. Such treatment would be especially advantageous for surfaces used in the making and using of pesticides, which comprise organophosphates. The expectation of success is high, as paints comprising enzymes are known in the art and the organophosphorus hydrolase of Cheng et al is active in a variety of compositions (Examples 4-7). Therefore, Claims 1, 15-27, 65-67, 72-75, 79-89, 94-100, 102, 110-119, 121-135, 180-182, 217, 219-242, 251-255, 272, 309, 319-321, 323, 324, 326, 327, 343-356, 360-362, 365-373, 376-385, and 389-392 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaventura et al, 1999 in view of Cheng et al, 1999, for the reasons stated above and in the prior action.

The prior rejection of Claims 81 and 251 under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Stoye et al, 1993, for the reasons explained in the prior action, is maintained. Claims 79, 80, 82-86, and 252-255 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Stoye et al, 1993, for the same reasons.

Claims 23, 25-27, 65-66, 226, 229, 230, 233-235, 326, and 309 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaventura et al, 1999 in view of Cheng et al, 1999 in light of what was well-known in the art: that OPH activity is regulated by Co2+ (23), that fragments and fusion proteins of enzymes having activity are useful (25-27), that enzymes can be targeted to cells using fusion proteins with binding motifs (65-66), that the compounds of Claim 226, 230, 233-235, and 326 can be used as pigments (226,229,230,233-235,326), that isolated enzymes can be stored in 50% glycerol (309).

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Mulbry et al, 1993. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising the OPH encoded by the Flavobacterium opd gene. Mulbry et al teach the OPH encoded by the Flavobacterium opd gene. It would have been obvious to a person of ordinary skill in the art to substitute the OPH of Cheng et al with the OPH of Mulbry et al. Motivation to do so derives from the desire to make and use a paint comprising an OPH. The expectation of success is high, as coatings comprising OPH were known in the art. Therefore, Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Mulbry et al, 1993.

Claims 99 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Burlant et al, 1969. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a binder that forms a film by cross-linking. Burlant et al teach binder that forms a film by cross-linking. It would have been obvious to a person of ordinary skill in the art to incorporate one or more binders of Burlant et al into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint having a wear-resistant surface. The expectation of success is high, as paints comprising binders were known in the art. Therefore, Claims 99 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Burlant et al, 1969.

Claims 133-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Panush et al, 1986. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a thermoplastic binder. Panush et al teach paint comprising thermoplastic binders. It would have been obvious to a person of ordinary skill in the art to incorprorate one or more thermoplastic binders of Panush et al into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint having higher adhesion to metal. The expectation of success is high, as paints comprising thermoplastic binders were known in the art. Therefore, Claims 133-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Panush et al, 1986.

Claims 239-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Waldron et al, 1992. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a biocide. Waldron et al teach paint comprising a biocide. It would have been obvious to a person of ordinary skill in the art to incorprorate the biocide of Waldron et al into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint having an activity to inhibit microbial growth. The expectation of success is high, as paints comprising biocides were known in the art. Therefore, Claims 239-242 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Waldron et al, 1992.

Claims 321, 345-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Krumhar et al, 1992. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a colormetric pH indicator. Krumhar et al teach a coating comprising the colormetric pH indicator Neutral Red. It would have been obvious to a person of ordinary skill in the art to incorprorate the colormetric pH indicator Neutral Red of Krumhar et al into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint having sensitivity to environmental pH, which would be advantageous in maintaining OPH activity. The expectation of success is high, as coatings comprising colormetric pH indicators were known in the art. Therefore, Claims 321, 345-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Krumhar et al, 1992.

Claims 348-350 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Gillette, 1995 (specification). The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a fluorimetric pH indicator. Gillette teaches several fluorimetric pH indicators. It would have been obvious to a person of ordinary skill in the art to incorprorate the fluorimetric pH indicators of Gillette into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint having sensitivity to environmental pH, which would be advantageous in maintaining OPH activity. The expectation of success is high, as coatings comprising colormetric pH indicators were known in the art. Therefore, Claims 348-350 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Gillette, 1995.

Claim 327 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Pusch et al, 1985. The combination of Bonaventura et al and Cheng et al is described above. Said combinaiton does not teach paint comprising a camouflage pigment that reduces detection by infrared. Pusch et al teaches a paint comprising a camouflage pigment that reduces detection by infrared. It would have been obvious to a person of ordinary skill in the art to incorprorate the camouflage pigment of Pusch et al into the paint rendered obvious by Bonaventura et al and Cheng et al. Motivation to do so derives from the desire to make and use a paint providing protections against detection by thermal imaging. The expectation of success is high, as paints comprising a camouflage pigment that reduces detection by infrared were known in the art. Therefore, Claim 327 is rejected under

35 U.S.C. 103(a) as being unpatentable over the combination of Bonaventura et al, 1999 and Cheng et al, 1999 in view of Pusch et al, 1985.

Allowable Subject Matter

No claims are allowable.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashhed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652